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Abstract. Arterial Spin Labeling (ASL) is a noninvasive perfusion technique which allows the absolute quantification for Cerebral Blood Flow (CBF). The perfusion is obtained from the difference between images with and without magnetic spin labeling of the arterial blood and the captured signal is around 0.5-2% of the magnitude of the labeling images, so the noise is one of the main problems for further data analysis. Classical method, *Mono-TI*, for CBF quantification is averaging repetitions with only one Inversion Time (TI) - the time delay between labeling and acquisition to allow the labeled blood to arrive the imaging slice. It improves the robustness to noise, however, cannot compensate the variety of Arterial Arrival Time (AAT). In this paper, *Diverse-TI* is proposed to exploit different TI sampling instants (sampling diversity) to improve the robustness to variety of AAT and simultaneously average repetitions with each TI (sampling repetitions) to improve the robustness to noise. Generally, the sampling diversity is relatively small and can be considered as compressed measurements, thus the Compressive Matched Filter (CMF) enlightened from sparsity is exploited to directly reconstruct CBF and AAT directly from compressed measurements. Meanwhile, regarding the CBF quantification performance, the compromise between the sampling repetition and sampling diversity is discussed and the empirical protocol to determine the sampling diversity is proposed. Simulations are carried out to highlight our discussions.

Keywords: ASL, CBF, Multi-TI, Diverse-TI, Compressive Matched Filter, Sparsity.

1 Introduction

The Arterial Spin Labeling (ASL) is an MRI (Magnetic Resonance Imaging)-based perfusion technique which uses the magnetically tagged water as a freely diffusible tracer to measure perfusion non-invasively. This blood water is first labeled with a radio-frequency pulse in the neck of the patient. After a delay, called Inversion Time (TI), which allows the labeled blood to arrive in the brain, a labeled image of the brain is acquired. A control image is also acquired without

labeling and the CBF estimation is done on the difference between the control and labeled image. For a fixed TI t, the perfusion signal is generally described by a kinetic model introduced by Buxton *et. al.* in [1]:

$$M_{\Delta}(t) = \begin{cases} 0, & t \in [0, \Delta) \\ 2\alpha f M_{0b}(t-\Delta) q_p(t) \exp(-t/T_{1b}), & t \in [\Delta, \Delta+\tau) \\ 2\alpha f M_{0b} \tau q_p(t) \exp(-t/T_{1b}), & t \in [\Delta+\tau, \infty) \end{cases} \tag{1}$$

where f is the CBF, α measures the labeling efficiency, M_{0b} is the equilibrium magnetization of arterial blood, Δ is the Arterial Arrival Time (AAT) to the interesting slice, τ is the temporal width of the bolus, T_{1b} is the relaxation time in blood and $q_p(t)$ is considered to be approximately equal to 1. Specifically, in QUIPSS II [2], a saturation pulse is given to the tagged bolus after a fixed period τ of the tagging time, thus the temporal width of the tagged bolus is known a priori.

The principle task of ASL analysis is quantifying the absolute value of CBF f. The traditional technique, which is called *Mono-TI*, only uses a single TI t after which the acquisition is gathered, where t is assumed to be bigger than $\Delta+\tau$ to guarantee a delay long enough to let the magnetic tagged blood arrive the interesting imaging slice. Then the quantification of CBF is a direct ratio between the magnetization difference M_{Δ} and the known terms, when $t > \Delta+\tau$.

However, two major problems prevent the efficiency of Mono-TI. At first, as the amplitude of the difference ASL signal is usually around 0.5-2% of the control image magnitude, its SNR is thus not sufficient for further analysis. Commonly, numbers of sampling repetitions are acquired for single TI (typically more than 30) and then averaged to improve the SNR. Secondly, the assumption $t > \Delta+\tau$ is not easy to be guaranteed in Mono-TI technique. Since Δ is varying between different patients, ages and physical situations. Even excluding these factors, the AAT is still an uncertain value due to the presence of laminar and turbulence flow, complicated vessel networks and cardiac pulsations [3]. This fact leads that the magnetic labeled blood may not have reached the imaging slice if the sampling time is too small and thus leads to underestimation of CBF. One possible way is giving the TI large enough, however, the magnetization difference M_{Δ} might be too small if TI is too big and thus leads to very low SNR.

In this paper, another measuring procedure with different sampling times is investigated for the CBF quantification, where the collected ASL data at different sampling times are captured during separate ASL RF pulse periods. It is different from the classical *Multi-TI* [4,5,6] and thus called *Diverse-TI* to avoid ambiguities. Multi-TI is a more recent and confidential sequence than Mono-TI and is not currently available on most MR-Scanners, while Diverse-TI proposed in this paper can easily be produced since it only uses regular ASL sequences. Before further analysis on real ASL data, the first and also the essential step is giving a protocol to concretely design the measuring procedures. It is clear that some issues should be preferentially considered: (1) *sampling repetition* (for the same sampling time), which is intended to improve SNR; (2) *sampling diversity* (sampling at different times) which is intended to compensate for the inexact

knowledge of parameters such as Δ, etc. For practical considerations, the most crucial criteria in real clinical studies is the *total measuring time* which is generally limited in a reasonable period. Thus the values of sampling repetition and sampling diversity can not be designed as large as possible to improve CBF quantification performance. A method to explicitly guide the design of these parameters is applaudable. However, to the best knowledge of the authors, the existing papers rarely focus on this point.

Consequently, as a preliminary study, the contribution of this paper is twofold. First, it formulates the considered problem as an instance of Compressive Matched Filter (CMF) [7]. Then, it numerically investigates the tradeoffs between repetition and sampling diversity (for the same total measurement time) on CBF estimation with CMF. In a word, the main question investigated in this paper is: given a total measurement time, shall we favor repetitions or sampling diversity?

2 Diverse-TI Technique

Since parameters including $\tau, T_{1b}, \alpha, M_{0b}$ and $q_p(t)$ are (or assumed to be) known a priori, the signal model (1) can be simplified as $M_\Delta(t) = f \times g(\Delta; t)$ where the time related term $g(\Delta; t)$ will be called "wave form" and can be defined by (1) with $f = 1$.

- Sampling Repetition
In practice, an important level of noise is affecting ASL measurements, hence the signal captured at time t can be expressed as follows:

$$y(t) = M_\Delta(t) + \epsilon(t) = f \times g(\Delta; t) + \epsilon(t)$$

where $\epsilon(t)$ is the noise term and is assumed to be Gaussian in this paper. In our setting, the measure at time t is repeated R times (sampling repetition), and averaging all measures divides the noise variance by R and thus it will improve the SNR according to the following equation:

$$Q_R = 10 \log_{10} R + Q_1 \tag{2}$$

where Q_1 is the SNR of one repetition and Q_R is the SNR after R repetitions.

- Sampling Diversity
Define $\boldsymbol{g}(\Delta) = \{g(\Delta, iT_s)\}_{i=1}^N$ where T_s is a reference regular sampling interval and $t_1 ... t_M$ (possibly irregular) time instants located on this regular grid, where $M \ll N$. With different TI (sampling diversity) $t_1 ... t_M$, the ASL data are respectively collected $\boldsymbol{y} \triangleq \{y(t_1), ..., y(t_M)\}^T \in \mathbb{R}^M$. Then we can write the sampling model in the form of linear operation:

$$\boldsymbol{y} = \Phi(f \times \boldsymbol{g}(\Delta) + \boldsymbol{\epsilon})$$

where $\Phi \in \mathbb{R}^{M \times N}$ is a sensing matrix, which verifies $\Phi\Phi^T = \boldsymbol{I}_M$.

At last, the task is to find the CBF parameter f and the optimal Δ that best match the observations $\boldsymbol{y}$. To fulfill it, Compressive Matched Filter (CMF) [7] is exploited in the following sections.

3 Compressive Matched Filter

In the case considered in this paper, the CBF quantification problem can be formed as a multiple detection problem to distinguish the following hypothesis:

$$\mathcal{H}_i : \boldsymbol{y} = \Phi(f\boldsymbol{g}(\Delta_i) + \boldsymbol{\epsilon}), \text{ with } i \in \{1, ..., d\}$$

where f is the CBF value, $\Delta_1, ..., \Delta_d$ are d possible AAT values that should be assumed before and $\boldsymbol{\epsilon} \sim \mathcal{N}(0, \sigma^2 \boldsymbol{I}_N)$ is the white noise term. In this case, the evidence under different hypothesis, for $i \in \{1, ...d\}$, can be written

$$p(y|\mathcal{H}_i) = \frac{\exp\left(-\frac{1}{2}(\boldsymbol{y} - \Phi f\boldsymbol{g}(\Delta_i))^T(\sigma^2\Phi\Phi^T)^{-1}(\boldsymbol{y} - \Phi f\boldsymbol{g}(\Delta_i))\right)}{(2\pi)^{N/2}|\sigma^2\Phi\Phi^T|^{1/2}}$$

Then the final detection is carried out by finding the hypothesis with the biggest conditional probability:

$$(f_s, \mathcal{H}_s) = \underset{f, \mathcal{H}_i, i\in\{1,...,d\}}{\arg\max} \; p(y|\mathcal{H}_i)$$

Thus by differentiating w.r.t. f, we can obtain its estimation

$$\hat{f}_i = \frac{\boldsymbol{y}^T(\Phi\Phi^T)^{-1}\Phi\boldsymbol{g}(\Delta_i)}{\boldsymbol{g}(\Delta_i)^T\Phi^T(\Phi\Phi^T)^{-1}\Phi\boldsymbol{g}(\Delta_i)} \tag{3}$$

and by taking logarithm we obtain an equivalent test that simplifies to

$$\begin{aligned}
\mathcal{H}_s &= \underset{\mathcal{H}_i, i\in\{1,...,d\}}{\arg\max} \left(\boldsymbol{y} - \frac{1}{2}\Phi\hat{f}_i\boldsymbol{g}(\Delta_i)\right)^T (\Phi\Phi^T)^{-1}\Phi\hat{f}_i\boldsymbol{g}(\Delta_i) \\
&= \underset{\mathcal{H}_i, i\in\{1,...,d\}}{\arg\max} \frac{1}{2}\frac{\left(\boldsymbol{y}^T(\Phi\Phi^T)^{-1}\Phi\boldsymbol{g}(\Delta_i)\right)^2}{\boldsymbol{g}(\Delta_i)^T\Phi^T(\Phi\Phi^T)^{-1}\Phi\boldsymbol{g}(\Delta_i)} \\
&\overset{\Phi\Phi^T=I}{=\!=\!=} \underset{\mathcal{H}_i, i\in\{1,...,d\}}{\arg\max} \left|\left\langle \boldsymbol{y}, \frac{\Phi\boldsymbol{g}(\Delta_i)}{\|\Phi\boldsymbol{g}(\Delta_i)\|_2}\right\rangle\right|
\end{aligned} \tag{4}$$

Above all, using (4) and (3), we can respectively obtain the estimation of arrival time $\hat{\Delta} = \Delta_s$ and the estimation of CBF $\hat{f} = f_s$.

4 Analysis and Simulations

Without loss of generality, the time used for one single sampling repetition can be assumed to be T_S, including the process of one time control imaging and tagging imaging. Then the total measuring time can be expressed as:

$$T = M \cdot R \cdot T_S \tag{5}$$

where M indicates the level of sampling diversity i.e. the number of TI and R the number of sampling repetitions. For practical considerations, the most crucial

criteria in real clinical studies is the total measuring time which is generally limited in a reasonable period. In one aspect, the sampling repetitions improve the signal SNR; while in the other aspect, the sampling diversity promote the robustness to the variety of AAT. Consequently, the compromise between the sampling diversity and sampling repetitions needs to be determined. In other words, given the maximum total time T, how to optimally choose R and M to reach better CBF quantification? To answer it, we first compare the extreme case when $M = 1$ to the other case when $M > 1$, then separately consider the case when $M > 1$.

4.1 Mono-TI technique v.s. Diverse-TI technique

In fact, $M = 1$ is exactly the Mono-TI technique. In order to well illustrate the performance of Mono-TI technique, a concrete simulation is carried on. In the following, the parameters of ASL model (1) are arbitrarily set as: $M_{0b} = 100, \alpha = 0.9, T_{1b} = 1.2s$ and $\tau = 1s$, and Fig. 1(left) shows one example when AAT $\Delta = 1$ and CBF $f = 10$ mL/(100g)/min. Obviously, given constant noise variance σ, the highest SNR of single repetition Q_1 is reached when $t_i = \Delta + \tau$ while it will decrease as t_i increasing.

The assumption on TI $t_i > \Delta + \tau$ is supposed to be verified. At first, t_i can not be much smaller than $\Delta + \tau$ otherwise the tagged blood can not reached the interest slice on time, as shown by the red diamond point in Fig. 1(left) when $t_i = 1s$; meanwhile, it can not be too big otherwise the captured signal will be too small which makes the SNR Q_1 very low, as shown by the green circle point in Fig. 1(left) when $t_i = 4.5s$. Then the CBF f can be calculated directly by $\hat{f} = y(t_i)/g(\Delta; t_i)$, however, the AAT Δ can not be estimated in Mono-TI technique.

Then Mono-TI technique is carried out in the following procedure. Fix the CBF $f = 10$ mL/(100g)/min, give one AAT value Δ, sample at the time t_i with noise corruption, and then one single repetition of the ASL signal is simulated. Without loss of generality, the time used for one single repetition is assumed $T_S = 5s$ (this value is set identically for all simulations). Then as an example, we can set the total time $T = 30$min, so according to (5) the Mono-TI technique allows $R = 360$ repetitions. According to (2), the SNR can reach to $Q_R = 30.56dB$ with $Q_1 = 5dB$. However, this value is very sensible to the sampling location, or equivalently, the AAT value. This fact can be well illustrated by Fig. 1, where the result of Mono-TI is obtained by fixing $t_i = 1s$, $3s$ or $4.5s$, then ranging AAT Δ from $0.1s$ to $3s$ (the performance shown in Fig. 1(right) is measured through the quantification SNR averaged over 1000 restarts). In Fig. 1, the result when $t_i = 1s$ shows the situation when TI is too short, $t_i = 4.5s$ shows the situation when TI is too long, even with proper TI $t_i = 3s$, the performance of quantification might largely decrease when AAT and the TI are mismatch.

In the framework of Diverse-TI , following the CMF algorithm, we first assess a large interval where the value of AAT should locate. In this simulation, this

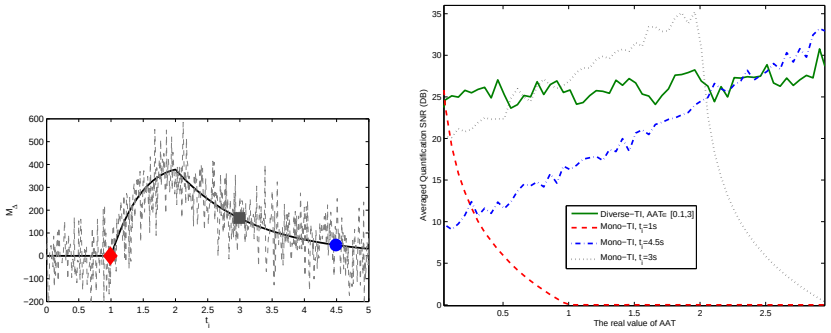

Fig. 1. (Left) Kinetic Model of ASL with $\Delta = 1$ ($\tau = 1s$) and $f = 10$ mL/(100g)/min (dark solid curve) and its noisy version with average SNR $5dB$ (grey dashed curve). (Right) Comparison between Mono-TI and Diverse-TI ($M = 10$) methods for different AAT with total time $T = 30$.

interval is set to $\Delta \in [0.1, 3]$. We choose the number[1] of sampling diversity to $M = 10$, and the sampling repetitions are set identically according to (5) with the same total time as Mono-TI, then the CBF quantification performances through CMF algorithm with different AAT value are obtained, as shown in Fig. 1. Diverse-TI can give constant performance which is also better than Mono-TI with a majority of AAT.

As a conclusion, in the case of $M = 1$, the CBF quantification quality might be better than $M > 1$, however, its performance is much sensitive to the sampling time, which is not easy to be designed practically. Moreover, as a supplement, Diverse-TI can also estimate the AAT.

4.2 Protocol to Sampling Diversity

In the last subsection, it has been shown that $M = 1$ is worse than $M > 1$, while in this subsection, we will propose a method to answer the question that how many sampling time locations are enough? Similarly, the total time T is the crucial parameter in clinical studies. Consequently, given a fixed total time T, the relationship between the CBF quantification performance and the number of sampling locations is essential to determine the required M.

In this simulation, the CBF f is fixed equal to 10mL/(100g)/min and the AAT Δ is randomly choosing from the interval $[0.1, 2]$, then the ASL signal are generated and corrupted by noises. Then to simulate the sampling procedure, the total time T is fixed respectively to $5, 10, 30, 60$min and the number of sampling time locations M is varying from 2 to 30, thus the number of repetitions R is determined via (5), then samples are collected. Since $\Delta \in [0.1, 2]$ is assumed, the CMF can be used to carry out the CBF quantification and AAT estimation, and the SNR of CBF quantification and AAT estimation are respectively shown

[1] This value is chosen according to empirical result, referring Fig. 2.

in Fig. 2 (bottom two figures). Meanwhile, the relationship between sampling repetition and sampling diversity can also be drawn according to (5), as shown in Fig. 2 (upper figure).

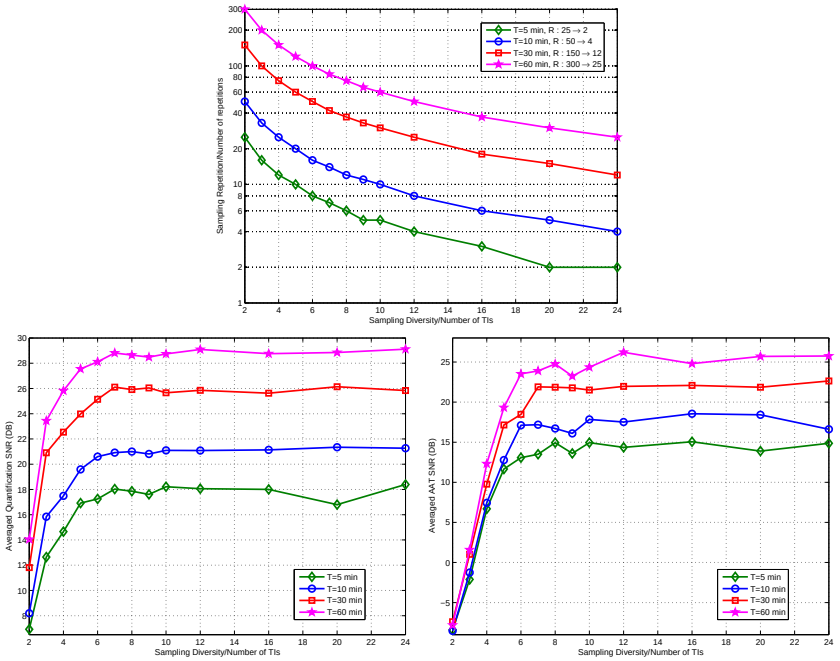

Fig. 2. Performance Evolution with respect to different sampling diversities M via CMF using different total time: CBF quantification (bottom left), AAT (bottom right) and sampling repetitions (up).

From the results, as expected, we can find that as M increases, the performance of Diverse-TI technique is improving before reaching an asymptotic value. From this simulation, we can find that the convergent point is around $M = 8$, as shown by the performance of CBF (or AAT) quantification in bottom figures of Fig. 2. Then according to (5), the repetitions at one sample time R can be calculated. It is worth mentioning that this simulation is only an example of choosing the number of multiple sampling time locations, for concrete applications, the curve in Fig. 2 should be re-drawn with appropriate parameters, and then the best value should be re-selected.

5 Conclusion and Future Works

Through this preliminary study, it is shown that the new Diverse-TI technique is superior to the classical Mono-TI technique, since the first can give steady CBF

performance and is capable to estimate the AAT. Furthermore, the sampling diversity of Diverse-TI technique has also been investigated where an experimental method is exploited and the protocol to design the sampling diversity, i.e. number of multiple sampling times, is proposed. Without loss of generality, from one exemplar simulation, we conclude that giving a total measuring time, the CBF quantification performance can be improved with the increase of the sampling diversity. Consequently, the sampling diversity should be designed large enough. On the other hand, when the sampling diversity is larger than a fixed value, the performance becomes constant. Thus, together with an upper bound resulted from the physical implementation constraints, the optimal region for sampling diversity can be well located through the proposed protocol.

The future works will consist in applying the parameter design protocol to guide the Diverse-TI technique in real ASL data acquisitions. Meanwhile, it is possible to extend CMF algorithm by considering additional priors to regularize the CBF estimation problem which might also improve the performance.

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